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Abstract: The aim of this study was to assess safety and efficacy of islet transplantation after initial pancreas transplantation with subsequent organ failure. Patients undergoing islet transplantation at our institution after pancreas organ failure were compared to a control group of patients with pancreas graft failure, but without islet transplantation and to a group receiving pancreas re-transplantation. 10 patients underwent islet transplantation after initial pancreas transplantation failed and were followed for a median of 51 months. The primary end-point of HbA1c <7.0% and freedom of severe hypoglycemia was met by 9 out of 10 patients after follow-up after islet transplantation and in all 3 patients in the pancreas re-transplantation group, but by none of the patients in the group without re-transplantation (n=7). Insulin requirement was reduced by 50% after islet transplantation. Kidney function (eGFR) declined with a rate of -1.0ml±1.2 ml/min/1.73m2 per year during follow-up after islet transplantation, which tended to be slower than in the group without retransplantation (p=0.07). Islet transplantation after deceased donor pancreas transplant failure is a method that can safely improve glycemic control and reduce the incidence of severe hypoglycemia and thus, establish similar glycemic control as after initial pancreas transplantation, despite the need of additional exogenous insulin.

DOI: https://doi.org/10.1111/ctr.13153

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Article type : Original Article

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Running Title

Islet transplantation after pancreas failure

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ctr.13153

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Key words

Islet transplantation, pancreas transplantation, type 1 diabetes mellitus, insulin

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Introduction

Whole organ pancreas transplantation has been performed in patients with type 1 diabetes mellitus in order to restore glycemic control for 50 years [1]. Initially, long-lasting insulin independence was often not achieved. However, nowadays insulin independence is routinely achieved in the majority of patients after pancreas transplantation and is still present in 60-70% of patients 5 years after transplantation [2]. In patients with loss of function of the transplanted pancreas, the question remains whether pancreas re-transplantation should be recommended, in particular in patients after combined pancreas-kidney transplantation with a functioning kidney graft and continued immunosuppression. In most patients, glycemic control worsens again after pancreas failure despite optimal medical care (intensive insulin treatment). However, there are also factors that may prohibit whole

organ re-transplantation, because patients are older than at the time of the first transplantation, and may suffer from additional cardiovascular complications that increase the risk of re-transplantation. In addition, re-transplantation may be technically more difficult in patients after previous abdominal surgery and with more advanced vascular disease. Pancreas transplantation, in contrast to kidney transplantation, is an intervention with a high complication rate. The reported rate of relaparotomy due to complications at the site of pancreas transplantation is about 30-40% of patients [3].

Islet transplantation is an alternative to whole-organ transplantation. This modality of transplantation was implemented by many centers mainly after the results of consistent insulin independence using a steroid-free immunosuppression protocol were published in 2000 [4]. While insulin independence is generally achieved in a lower number of cases after islet transplantation [5] as compared to pancreas transplantation in most centers, good glycemic control comparable to whole-organ transplantation can be routinely achieved with a much lower rate of complications [6, 7]. In addition, the results of islet transplantation have considerably improved in recent years [8, 9].

Thus, islet transplantation after initial pancreas transplantation and pancreas organ failure may be considered as an alternative to re-transplantation of the whole organ.

The aim of this study was to evaluate the safety and efficacy (HbA1c <7.0% and freedom of severe hypoglycemia) of islet transplantation after donor pancreas failure in pancreas transplantation.

Patients and Methods

Study design

All patients who underwent islet transplantation alone (ITA) or simultaneous islet-kidney transplantation (SIK) at the University Hospital Zurich between January 1st 2000 and December 31st 2015 after initial pancreas transplantation with pancreas organ failure were included in the study, as well as 7 patients with pancreas organ failure but no consecutive re-transplantation and three patients who received pancreas re-transplantation as a control group. The possibility of pancreas- or islet re-transplantation was discussed with patients suffering from pancreas donor organ failure after initial transplantation at our institution. The decision regarding possible pancreas- or islet-re-transplantation was made after considering the patient's preference as well as age and comorbidity.

Data of follow-up after islet transplantation was collected prospectively; data of follow-up after pancreas transplantation was collected prospectively after 2000 and retrospectively for patients who received a pancreas graft before 2000.

The primary end-point was the achievement of HbA1c < 7.0% and freedom from severe hypoglycemic events as suggested by our group in 2008 [10] and used in the CIT Trials [9].

The study protocol was reviewed and approved by members of the board of trustees of the University Hospital of Zurich Transplantation Centre. After 2008, patients were simultaneously included in the Swiss Transplant Cohort Study. Written informed consent was obtained from study participants prior to surgery/intervention.

Patient selection for transplantation

Patient selection for islet-after-pancreas transplantation (vs. pancreas re-transplantation or best medical care) was performed after careful evaluation of possible advantages and

disadvantages, with special regard to age and comorbidities. Patients considered being at higher risk for intra-operative complications were preferentially assigned to the less invasive procedure of islet transplantation, while only younger and healthier patients were offered both modalities (islet transplantation or pancreas re-transplantation).

Assessment of diabetes related complications and cardiovascular risk factors

Retinopathy was defined according to the diagnosis made by ophthalmological examination. Peripheral neuropathy was defined by clinical examination, using the Michigan Neuropathy Screening Instrument (MNSI, [11]), monofilament pressure sensation and electrodiagnostic testing in atypical cases. Autonomic neuropathy was diagnosed by the history and clinical examination, which included computer analysis of heart rate variability (ProSciCard, CPS GmbH, Wetzlar, Germany). Macrovascular disease was assessed by patient history, physical examination and angiography results.

Severe hypoglycemia was defined as any hypoglycemic event that required assistance from another person to treat or loss of consciousness.

Biochemical analyses

HbA1c was measured with the DCA 2000 (Bayer Diagnostics, Elkhart, USA) according to the manufacturer's instructions. Plasma C-peptide was measured with an IRMA kit (Technogenetics, CIS Bio International, Schering, Baar, Switzerland) with a local laboratory intra-assay and inter-assay coefficient of variation of 4.7% and 5.6%, respectively, and a lower limit of detection of 12 pmol/l. Cholesterol was measured by an enzymatic colorimetric test using cholesterol esterase and cholesterol oxidase, triglycerides were determined by a colorimetric reaction with iodonitrotetazolium chloride after enzymatic hydrolysis (modular P lab analyzer, Roche, Switzerland). HDL cholesterol was measured by a homogeneous

enzymatic test (Cobas Integra lab analyzer, Roche, Switzerland) and LDL cholesterol concentration was calculated with the Friedewald formula [12].

Organ procurement and transplantation procedure

Kidneys and pancreata were obtained from brain-dead multi-organ deceased donors from different hospitals in Switzerland. Written informed consent was given by the closest relatives. Panel reactive antibodies (PRA) were measured at the time of activation for the transplantation waiting list and included in the decision whether to accept a certain organ for transplantation or not. A negative serum cross-match between donor and recipient and AB0 compatibility were considered as minimal requirements for transplantation.

Preparation and transplantation of the pancreatic islets were performed as described previously [13]. Transplanted islets were not cultured before transplantation. Islet transplantation was conducted by a transhepatic percutaneous approach. Islet volume is given as islet equivalents (IEQ) [14] and islet number.

Pancreas organ failure was defined as C-peptide (stimulated) of less than 100pmol/l, and/or HbA1c >8%.

Immunosuppression

Immunosuppression after initial pancreas transplantation included a regimen with tacrolimus [15] and mycophenolate mofetil [16], as well as prednisone. Induction therapy was performed initially with basiliximab, later with thymoglobuline [17]. Target trough levels for tacrolimus were initially 10-15 µg/l, and long-term 6-8ug/l. Mycophenolate mofetil was administered weight adapted twice daily in doses of 720-1440mg.

For islet transplantation, the immunosuppression was carried out initially with tacrolimus and sirolimus (Wyeth Pharma, Zug, Switzerland), according to the Edmonton protocol [4], but changed after 2012 to the same regimen as for pancreas transplantation due to the high rate of side effects reported for sirolimus [5], now including the use of steroids for 4 days (starting with a bolus of 500mg prednisone before the intervention, to a dosage of 25mg on the last day). For induction, thymoglobuline was used for the first transplantation (if thymoglobuline was not used before), and basiliximab afterwards. In addition, etanercept was used (50mg before transplantation; 25mg on day 2, 7 and 10 after transplantation) [18].

Follow-up after transplantation

During follow-up after transplantation, transplant function was assessed by HbA1c measurement and need for exogenous insulin (insulin requirement U/kg of body weight). C-peptide secretion was assessed in patients after islet transplantation only during a mixed-meal tolerance test (6 kcal/kg body weight, energy sources: 54% carbohydrates, 29% fat, 17% protein; measurements every 30 min for 180 min) at least every year after transplantation. Renal function was assessed by serum creatinine and GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration formula [19]. Patients were seen at least every 3 months for evaluation of transplant function and adverse events and adaptation of insulin therapy if necessary. For assessment of cardiovascular risk, blood pressure, triacylglycerols, total cholesterol and both HDL-and LDL-cholesterol were measured, in addition to glycemic control. All patients were treated according to current international guidelines. In particular, insulin treatment after transplantation, if necessary, was carried out with the same regimen and intensity as before transplantation. Every patient with an HbA1c ≥ 6.5% was treated with insulin. Severe hypoglycemia was defined as a hypoglycemic episode with the requirement of assistance of another person (including loss of consciousness). If HbA1c levels above 7% persisted, and / or in case of recurrent severe

hypoglycemia after islet transplantation, the possibility of an additional islet transplantation was offered to the patient.

Statistical analysis

Data are presented as means ± SD, median and range, or relative frequencies. For comparison of continuous variables in two related groups the Wilcoxon test was applied, for comparison of independent groups the Kruskal-Wallis test was used. For the analysis of categorical frequency data, the $\chi 2$ and Fisher exact probability procedures were applied. A value of $p < 0.05$ was considered significant. All calculations were performed using SPSS® Statistics software Version 24 (IBM, Armonk, USA).

Results

Patient and transplant characteristics

A total of 10 patients received islet transplantation after organ function failure of the transplanted pancreas after SPK transplantation (group 1). For comparison, seven patients with pancreas failure after SPK transplantation, but without re-transplantation, were included in the analysis (group 2). Further data of a smaller group (n=3, group 3) of patients with pancreas re-transplantation was also included in the analysis.

Time between pancreas transplantation and pancreas organ failure was 2 months in group 1 (median; range: 0-6.9 years), 11 months in group 2 (range: 0-5.9 years; ns), and 2 months in group 3 (range: 0-0.8 years; ns). Two patients in group 1 and 2, an one patient in group 3 lost the organ within the first month after transplantation. The reasons for pancreas organ loss in the three groups were acute rejection (1 patient in group 1 and 2), chronic rejection (4, 2 and 1 patient in the 3 groups, respectively) and vascular causes (5,4 and 1 patient).

Baseline characteristics of patients are described in table 1. Duration between pancreas and islet transplantation was 6.1 years (median, range: 1.9 – 29.4 years), between pancreas and pancreas re-transplantation 1.1 years (0.5 – 7.7 years). At the time of islet transplantation, 9 out of 10 patients presented with an HbA1c > 7.0% (3 out of 3 patients in the pancreas re-transplantation group), and the occurrence of severe hypoglycemia was registered in 7 patients (2 in the pancreas re-transplantation group).

Transplant characteristics including number of islet infusions, transplanted islet number and volume (IEQ/kg body weight) are also shown in table 1. The mean number of transplantations was 1.6 ± 1.3 per patient.

The 16 islet donors had a mean age of 56.8 ± 10.1 years, the 3 pancreas (re-transplantation) donors an age of 38.9 ± 5.1 years ($p<0.01$). Donor age of the initial pancreas transplantation: 36.1 ± 12.7 years in group 1, 27.0 ± 11.3 years in group 2 and 42.3 ± 9.0 years in group 3, ns. 52.6% of islet donors were females; BMI of islet donors was 28.1 ± 5.7 kg/m^2 (for pancreas re-transplantation donors: 66.7% females, BMI 24.5 ± 0.4 kg/m^2).

Panel reactive antibodies (PRA) were measured ≥ 0% in 2 of the 10 islet recipients (7% and 61%) at the time of waiting-list activation for islet transplantation.

Mean follow-up after islet transplantation was 51 months (median, range 7 to 142 months), and 34 months after pancreas re-transplantation (30 to 36 months, ns). Total follow-up after initial pancreas transplantation was 11.8 years (median, range 6.8 to 31.7 years) in group 1, 9.0 years (5.1 to 11.0) in group 2 and 4.1 years (3.0 to 9.6) in group 3 (ns).

Diabetes related and macrovascular complications, hypertension, smoking

Proliferative retinopathy was present in 80%, 100% and 100% of patients at baseline in groups 1, 2 and 3, respectively (ns). All patients suffered from end-stage renal disease. Peripheral and/or autonomic neuropathy were present in 90%, 100% and 100% of patients

in the three groups (ns). 70%, 70% and 67% in the three groups suffered from cardiovascular disease (ns), 70%,100% and 67% had arterial hypertension (ns). Two patients in group 2 were smokers.

Glycemic control and incidence of hypoglycemia

The primary end point of HbA1c < 7.0% and freedom of severe hypoglycemia was successfully met by all patients after islet transplantation at 1 year and 90% at the end of follow-up (group 1), but by none of the patients without re-transplantation (group 2) ($p<0.001$). In group 3 (pancreas re-transplantation), the primary end point was met by all patients after re-transplantation and at the end of follow-up.

Glycated hemoglobin (HbA1c) decreased after pancreas transplantation by 2.5% from baseline (8.5 ± 1.8%) to 6.0 ± 0.3% in group 1, by 2.0% from baseline (7.8 ± 1.1%) to 5.8 ± 0.9%in group 2 ($p<0.05$ for both), and by 2.6% from baseline (7.7 ± 1.7%) to 5.1 ± 0.4% in group 3 (ns). However, it increased again after pancreas transplant failure. After islet transplantation, HbA1c decreased from 8.0 ± 1.4% to 6.0 ± 0.5% ($p<0.001$) and remained stable during follow-up (HbA1c at the end of follow-up: 6.2 ± 0.8%), whereas a reduction of HbA1c could not be achieved with best medical treatment in group 2, where HbA1c values remained above 8% during follow-up, and was 8.3% at the end of follow-up (figure 1). After pancreas re-transplantation (group 3), HbA1c decreased from 8.2 ± 0.7% to 5.6 ± 0.3%, with a value of 5.9 ± 0.7% at the end of follow-up.

Insulin independence was achieved in 2 patients after islet infusion, but insulin therapy became necessary in all recipients at the end of follow-up. Insulin requirements and maximally stimulated C-peptide levels were 0.62 ± 0.18 U/kg body weight (41.2 ± 19.5 U total) per day and 129 ± 223 pmol/l before islet transplantation (with only 2 out of 10 patients being C-peptide positive (> 100 pmol/l)). After islet transplantation, insulin requirements and stimulated C-peptide were 0.28 ± 0.23 U/kgBW/d (19.9 ± 20.2 U total) and 1444 ± 922 pmol/l

during follow-up, and at the end of follow-up they were 0.38 ± 0.28 U/kgBW/d (26.6 ± 25.7 U total) and 840 ± 775 pmol/l (figure 2). Both the decrease of insulin requirement ($p<0.001$) and the increase in stimulated C-peptide ($p=0.02$) were statistically significant. 9 out of 10 patients were still C-peptide positive (>100pmol/l) at the end of follow-up.

In contrast, insulin requirements were high in group 2 after pancreas failure (0.75 ± 0.39 U/kg/d body weight, 48.8 ± 20.3 U total) and remained high during follow-up (end of follow-up: 0.74 ± 0.49 U/kg/d body weight, 46.9 ± 27.4 U total, ns).

In group 3, all patients became insulin independent after pancreas re-transplantation, and insulin independency was preserved until the end of follow-up (with a mean HbA1c of < 6% during follow-up as described above; HbA1c one year after transplantation: 5.7 ± 0.4%).

The frequency of severe hypoglycemia decreased from 120 to 5 per 100 patient years after islet transplantation (occurring in one patient with negative C-Peptide) ($p=0.03$), and from 70 to 0 per 100 patient years after pancreas re-transplantation.

Cardiovascular risk factors and kidney function during follow-up

Weight, kidney function, blood pressure and serum lipid levels are shown in table 2. Significant changes observed after islet transplantation were reductions of LDL cholesterol (end of follow-up) and of triglyceride levels (initially after transplantation).

Kidney function in terms of eGFR declined with a rate of -1.0 ml ± 1.2 ml/min/1.73m^2 per year during follow-up after islet transplantation, with a starting eGFR at the time of islet transplantation of 48.2 ± 14.1 ml/min/1.73m^2. The decline of eGFR in group 2 with no re-transplantation was -2.7 ± 2.3 ml/min/1.73m^2 per year during follow-up ($p=0.07$). In group 3, eGFR declined with a rate of -1.2 ± 1.7 ml/min/1.73m^2 per year during follow-up after pancreas re-transplantation.

Side effects of islet transplantation

There was no need for surgical intervention after any of the islet infusion procedures. All patients received immunosuppression primarily for the transplanted kidney and there were no short-term side effects that could be attributed to the change in immunosuppression (induction therapy).

In one of the three patients after pancreas re-transplantation, revision surgery (re-laparatomy) due to hematoma had to be performed.

Discussion

Our study evaluated the effect of islet transplantation in a cohort of patients with failed pancreas organ function after combined pancreas-kidney transplantation with a long-term follow-up of more than 4 years. This cohort was compared to a second cohort receiving no re-transplantation after pancreas organ failure, and to three patients receiving pancreas re-transplantation after failure of function of the initially transplanted pancreas.

Studies on the outcome of pancreas re-transplantation after failure of pancreas organ function have revealed conflicting data. Some studies in small cohorts (number of re-transplantations: 18-37) reported a similar rate of graft survival after pancreas re-transplantation compared to the initial transplantation [20-22]. However, a recent study in the large Minnesota cohort (415 re-transplantations) demonstrated an increased rate of organ failure in pancreas re-transplantation; a multivariate analysis revealed increasing pancreas transplant number to result in a hazard ratio of 1.78 (for second transplants) and 2.42 (for third and fourth transplants) [23]. Also, analysis of data from the United Network for Organ Sharing (UNOS) database including 19705 primary transplants and 1149 re-transplantations came to a similar conclusion, with a graft survival rate at 5 years of 69.2% (primary transplantation) versus 14.5% (re-transplantation) [24].

As patient mortality and technical failure were not increased after pancreas re-transplantation in the large Minnesota cohort, pancreas re-transplantation can be considered a procedure as safe as the first transplantation [23]. However, it is important to point out that the mean recipient age in this cohort was less than 45 years. Higher patient age, with an increased disease burden and frequency of cardiovascular morbidity and vascular disease, may increase technical problems as well as the complication risk in pancreas re-transplantation. Thus, it is presently not known, whether pancreas re-transplantation can be considered to be safe also in older recipients like the ones evaluated in our study, with a mean age of more than 52 years.

As demonstrated here, islet transplantation after failed pancreas transplantation was a safe procedure in these 10 older patients, with a diabetes duration of more than 40 years at transplantation and established cardiovascular disease in 7 out of 10 patients.

Importantly, with a mean of 1.6 islet transplantations per recipient, it was possible to lower HbA1c to levels similar to those after initial pancreas transplantation (and similar to those after pancreas re-transplantation in the third group) and to reduce the incidence of severe hypoglycemia by more than 20fold to a rate that was much lower than the one reported for patients receiving intensive or even less intensive insulin treatment in the DCCT [25] or in our own cohort [26], where HbA1c levels were substantially higher than in patients after islet transplantation as described here. This improvement was observed despite a need for some exogenous insulin in all patients at the end of follow-up. Thus, we conclude that even low levels of endogenous insulin as observed in our cohort (positive C-peptide response in 9 of 10 patients) are sufficient to support exogenous insulin therapy in order to facilitate glucose control and prevent severe hypoglycemia by more than 95%, obtaining similar results as compared to whole organ pancreas transplantation. The insulin requirement was 38% less than before transplantation at the end of follow-up. Of course, islet transplantation has to be seen as part of a multimodality approach, and optimal support regarding insulin therapy is necessary in order to achieve good glycemic control. On the other hand, even optimal

conservative therapy (as provided to the group without re-transplantation) was not sufficient to achieve good glycemic control when not supported by a certain amount of endogenous insulin production.

The primary end point of good glycemic control (HbA1c < 7%) and avoidance of severe hypoglycemia one year after transplantation was achieved in a high proportion of patients (90%) that was similar to the primary outcome of the recently published trial of the CIT Consortium (88% of patients) [9], with a slightly lower number of IEQ transplanted per kg patient weight in our study. In contrast, it was not possible to achieve HbA1c levels below 7% in any patient in the control group without islet transplantation after pancreas failure. The insulin dosage that was necessary after transplantation was higher in our study compared to the CIT trial. Besides the lower amount of transplanted IEQ, this might also be due to a higher proportion of sensitization in patients after pancreas transplantation (in particular with some patients who lost function of the organ due to rejection) and thus, a higher amount of loss of transplanted islets by rejection.

When compared to the earlier published results of the whole cohort of patients receiving islet transplantation at our center [7], glycemic control was slightly better in patients described here with islet after pancreas transplantation (HbA1c of 6.2% vs. 6.5%). The two patients with PRA levels >0% showed a tendency towards a somewhat higher HbA1c at the end of follow-up (6.6% vs. 6.1%), but the low number of these patients prohibits any conclusions. Further comparison of HbA1c levels that were achieved in our cohort after islet-transplantation with those of patients receiving pancreas re-transplantation in cohorts from other centers reveals only slightly higher HbA1c values (HbA1c of around 6% during follow-up, compared with levels around 5.5% described in [22]).

Further, a good glucose control could be achieved despite a relatively high donor age (compared to the whole organ donors). The older donor age is mainly due to the allocation criteria in Switzerland, where organs of younger donors are preferentially used for whole organ transplantation.

It was previously shown that islet transplantation may slow down the progression of nephropathy [27] and neuropathy [28]. In the light of the high rate of already established diabetes complications at baseline, we did not evaluate the progression of complications in this study, with the exception of renal function of the transplanted kidney. We observed a decline in eGFR of -1.0 ml/min/1.73m^2 per year, which is similar to the rate that is observed in pancreas transplantation at our institution [7] as well as by other groups [29]. In the group without islet transplantation, eGFR decline was higher (albeit not statistically significant). Body weight and cardiovascular risk factors as blood pressure and serum lipids remained stable after islet transplantation.

Although the small number of islet recipients studied represent a clear limitation, we believe that it is of importance to address the issue of re-transplantation for this very specific population (pancreas organ failure and re-transplantation at relatively high age, with high perioperative cardiovascular risk due to coronary heart disease), which we believe to be small in most centers performing pancreas and islet transplantation. Even if the follow-up time of 4 years might be considered relatively short, we have individual observation times of up to 12 years and a long duration after kidney transplantation, which is likely to be sufficient to demonstrate safety and efficacy of islet transplantation after pancreas organ failure. Nonetheless, it has to be mentioned that some possible side-effects, e.g. long-term effects of induction therapy, could not be assessed within the follow-up of our study since this would need a longer observation time.

A recent publication reported results of islet after combined or sequential pancreas-kidney transplantation (as well as pancreas after islet transplantation) [30]. However, this study included only 3 transplanted patients with a younger mean age (39.7 years). There was only one older patient (52 years), and this patient showed persistent high blood glucose levels after islet transplantation (HbA1c 12.1% at the end of follow-up). Thus, we believe that our study extends the current knowledge with important information regarding the safety and efficacy of islet after pancreas transplantation also in a cohort of older patients.

In summary, we were able to demonstrate in this study that islet transplantation after failed initial pancreas transplantation is a method that can safely improve glycemic control (HbA1c < 7%) and reduce the incidence of severe hypoglycemia. It is able to establish comparable glycemic control as after initial pancreas transplantation (despite the need of additional exogenous insulin after islet transplantation) and to protect the transplanted kidney from re-occurrence of diabetic nephropathy.

Acknowledgements

We thank E. Bernhard-Roth, I. Kehret and H. Seiler (all Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich) for their assistance. Philipp A. Gerber was supported by the Promedica Foundation and the Foundation of Diabetes Research at the University Hospital Zurich.

Author contributions

Philipp A. Gerber: Research design, performance of the research, data analysis, discussion, writing of the paper

Michel Hochuli: Performance of research, data analysis, discussion

Bara D. Benediktsdottir: Performance of research, data analysis, writing of the paper

Richard A. Zuellig: Performance of the research, discussion

Oliver Tschopp: Performance of the research, discussion

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Christian Oberkofler: Performance of the research, discussion

Giatgen A. Spinas: Research design, writing of the paper

Roger Lehmann: Research design, performance of the research, data analysis, discussion, writing of the paper

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Tables

Table 1: Patient and transplantation characteristics

Characteristic	Group 1	Group 2	Group 3	p
Number of patients	10	7	3	
Female (%)	30.0	42.9	100	0.10
Age at diabetes diagnosis (y)	12.1 ± 7.3	9.7 ± 5.3	12.8 ± 1.1	0.67
Age at pancreas transplantation (y)	41.0 ± 10.6	41.4 ± 2.7	35.6 ± 9.5	0.59
Age at islet (pancreas re-) transplantation (y)	52.2 ± 6.0	n/a	38.4 ± 6.7	0.03
Number of islet transplantations (n)	1.6 ± 1.3	n/a	n/a	
Total islet number per kg body weight (n)	9405 ± 9547	n/a	n/a	
Total islet equivalent per kg body weight (IEQ)	9676 ± 9785	n/a	n/a	

Data are given as Mean ± SD or %. Group 1: Patients with islet transplantation after pancreas organ failure, group 2: Patients with pancreas failure but without re-transplantation, group 3: Patients with pancreas failure and pancreas re-transplantation. p: p-value for statistical difference between the three groups..

Table 2: BMI, Kidney function, cardiovascular risk factors

Parameter		Before PTPL	After PTPL	After PTPL Failure	Before ITPL / PRTPL	After ITPL / PRTPL	End of follow-up
BMI (kg/m^2)	Group 1	23.5 ± 4.5	24.3 ± 6.1	24.2 ± 5.6	24.2 ± 5.0	23.8 ± 4.6	24.1 ± 5.4
	Group 2	23.4 ± 3.2	22.6 ± 2.5	23.2 ± 2.6			24.1 ± 3.0
	Group 3	21.2 ± 1.3	21.3 ± 1.5	21.7 ± 1.5	21.7 ± 1.8	21.8 ± 1.7	21.9 ± 2.0
eGFR (ml/min/1.73m^2)	Group 1	14.0 ± 7.0	60.5 ± 21.0†	51.1 ± 14.6†	48.2 ± 14.1†	47.2 ± 18.2†	43.2 ± 19.8†
	Group 2	9.4 ± 4.6	77.6 ± 31.1†	75.4 ± 30.3†			57.5 ± 27.4†
	Group 3	10.0 ± 5.7	64.5 ± 0.7	56.5 ± 4.9	63.5 ± 3.5	62.5 ± 3.5	59 ± 1.4
Total cholesterol (mmol/l)	Group 1	4.5 ± 1.0	4.3 ± 2.1	4.8 ± 1.8	4.7 ± 1.1	4.3 ± 1.4	4.1 ± 1.5
	Group 2	4.2 ± 0.7	4.4 ± 1.0	4.6 ± 1.2			4.7 ± 1.0
	Group 3	4.3 ± 1.3	4.5 ± 0.1	5.3 ± 0.1	5.0 ± 0.5	5.0 ± 0.4	4.8 ± 0.1
LDL cholesterol (mmol/l)	Group 1	2.0 ± 0.1	2.4 ± 1.7	2.1 ± 1.1	2.4 ± 0.7	2.0 ± 0.7	1.8 ± 0.8§
	Group 2	2.3 ± 0.7	2.5 ± 0.9	2.7 ± 1.0			2.3 ± 0.5
	Group 3	2.2 ± 1.1	2.3 ± 0.7	2.6 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.4 ± 0.5
HDL cholesterol (mmol/l)	Group 1	1.5 ± 0.4	1.6 ± 0.1	1.5 ± 0.6	1.4 ± 0.6	1.5 ± 0.5	1.3 ± 0.5
	Group 2	1.1 ± 0.3	1.0 ± 0.3*	0.9 ± 0.1			1.1 ± 0.4
	Group 3	1.8 ± 0.1	1.4 ± 0.2	2.0 ± 0.4	2.0 ± 0.4	1.9 ± 0.1	1.8 ± 0.4
Triglycerides (mmol/l)	Group 1	2.1 ± 0.8	1.7 ± 0.6	1.7 ± 0.8	1.9 ± 1.3	1.4 ± 0.9§	1.7 ± 0.9
	Group 2	1.4 ± 0.4	2.0 ± 1.1	2.3 ± 1.0			1.8 ± 1.1
	Group 3	0.9 ± 0.7	1.7 ± 1.0	1.8 ± 1.3	1.7 ± 1.3	1.3 ± 0.3	1.0 ± 0.4
Systolic blood pressure (mmHg)	Group 1	148 ± 23	146 ± 20	134 ± 24	132 ± 25	139 ± 24	130 ± 13
	Group 2	155 ± 36	137 ± 16	144 ± 11			140 ± 19
	Group 3	148 ± 4	133 ± 11	153 ± 11	140 ± 7	133 ± 11	125 ± 7
Diastolic blood pressure (mmHg)	Group 1	87 ± 15	86 ± 11	83 ± 14	77 ± 16†	81 ± 8	75 ± 8*
	Group 2	80 ± 18	83 ± 14	83 ± 18			83 ± 7*
	Group 3	88 ± 4	85 ± 7	83 ± 11	83 ± 4	80 ± 7	78 ± 4*

PTPL: pancreas transplantation; ITPL: islet transplantation; PRTPL: pancreas re-transplantation. * Significant difference between groups ($p<0.05$). † Significantly different compared with levels before pancreas transplantation ($p<0.05$). § Significantly different compared with levels before islet (or pancreas re-) transplantation ($p<0.05$).

Figure legends

Figure 1. Median HbA1c (%, 1./3. Quartile, Range) before and after pancreas transplantation, after pancreas failure and during follow-up after re-transplantation in patients with (group 1, bright grey bars) and without consecutive islet transplantation (group 2, white bars), as well as in patients with pancreas re-transplantation (group 3, dark grey bars). PTPL: pancreas transplantation; ITPL: islet transplantation; PRTPL: pancreas re-transplantation. * = significantly different from baseline, $p<0.05$. † = significant difference between groups, $p<0.01$.

Figure 2. Median C-peptide levels (A) and insulin requirement (B) (1./3. Quartile, Range) before and after islet transplantation (ITPL). * = different from baseline, $p<0.05$.